sciendo

10.2478/AMB-2025-0001

ORIGINAL ARTICLE

ANEMIA IN NEWLY DIAGNOSED CASES WITH LIVER CIRRHOSIS

M. Mihaylova[1], S. Strashilov[2], P. Tonchev[3]

[1]Department of Gastroenterology, Nephrology and Hematology, Faculty of Medicine, Medical University of Pleven, University Hospital Georgi Stranski – Pleven, Bulgaria
[2]Department of Plastic Restorative, Reconstructive and Aesthetic Surgery, Medical University – Pleven, Bulgaria
[3]Department of Surgical Nursing Care, Faculty of Health Care, Medical University – Pleven, Bulgaria

Abstract. *Between 50% and 87% of cases with liver cirrhosis have a concomitant anemic syndrome, which is the most common hematological abnormality on routine examination.* ***Aim:*** *To determine the frequency, type and severity of anemia in newly diagnosed cases with liver cirrhosis.* ***Materials and methods:*** *A retrospective study of newly diagnosed cases of liver cirrhosis was performed for the period 2017–2021. The study group included 361 individuals, of whom 258 (71%) were men and 103 (29%) women. The mean age was 57 ± 11.4 years. The main etiology was alcohol consumption in 262 (72.5%) of them. All were graded by Child-Pough score. MELD Na of each was calculated. Results were processed with IBM SPSS 26 and Excel statistics. We used ANOVA, Mann-Whitney, and Pearson Chi-Square tests at a certain level of statistical dependence and a p-value less than 0.05.* ***Results:*** *Of the entire study population, 258 (71%) were found to be anemic, and mild anemia was found in 160 (62%) of them. The most common was normocytic anemia in 135 (52.3%) of the cases. Macrocytic anemia was found in 88 (34.1%) of the cases, which shows a significant dependence on alcohol etiology. Microcytic anemia was found in 35 (13.56%) of the cases. We confirmed a statistically significant difference in Child-Poug score (p = .000) and MELD Na score (p = .002) in cases without and with anemia.* ***Conclusion:*** *Anemia is the most common hematological manifestation in liver cirrhosis.*

Key words: *Child-Pough, hemoglobin level, MCV, MELD Na*

Corresponding author: *Miroslava Ivanova Mihaylova, 8A Georgi Kochev blvd, University Hospital Georgi Stranski, Pleven 5800, Bulgaria, tel: +359 887 13 16 21, e-mail: mihailova75.md@gmail.com*

ORCID: *0000-0001-7960-4373*

Received: *28 June 2024;* ***Revised:*** *25 November 2024;* ***Accepted:*** *18 December 2024*

INTRODUCTION

Between 50% and 87% of cases with liver cirrhosis have anemia, which is the most common hematological abnormality in routine examination [1]. Its occurrence is associated with worsening prognosis in compensated cases [2]. A hemoglobin (Hb) value below 100 g/L is associated with progression of portal hypertension [3, 4] and subsequent liver decompensation [3]. A higher rate of hospital readmission [5] and increased short-term mortality [3, 6] have been observed in these patients. The presence of anemia worsens the accompanying ascites, as well as causes renal dysfunction, due

to the hypoxia and hypoperfusion present [4]. The role of an aggravating factor in cases with persistent portosystemic encephalopathy has also been established [7]. The occurrence of anemia in cirrhosis is a multifactorial process. Acute and chronic bleeding from GIT (gastrointestinal tract), deficiency of vitamin B12, B6 and folic acid, poor nutrition especially in cases with alcoholic etiology, as well as the manifestation of hypersplenic syndrome are discussed as the most common causes of the occurrence, although erythrocytes (Er) are least affected [1].

Objective: To determine the frequency, type and severity of anemia in a population of newly diagnosed cases with liver cirrhosis.

MATERIALS AND METHODS

This was a retrospective study of newly diagnosed hospital cases of liver cirrhosis for the 5-year period from 2017 to 2021. Overall, 361 individuals over the age of 18 were included. Exclusion criteria were previous, recent or current bleeding as well as recent blood transfusion. The necessary information was collected from the patients' hospital records at their first admission. The research was conducted in accordance with the ethical standards of the Declaration of Helsinki. The diagnosis was made by a standard panel of clinical, laboratory and instrumental methods. Of all, 258 (71%) were men and 103 (29%) were women. Age of the studied population was 57 ± 11.4 years. In 262 (72.5%) of them the leading etiology was alcohol alone or in combination with chronic viral hepatitis B and C. Child-Pough score [https://www.mdcalc.com/calc/340/child-pugh-score-cirrhosis-mortality] and MELD Na score [https://www.mdcalc.com/calc/10437 model-end-stage-liver-disease-meld?] were calculated.

In Child A there were 98 (27%), in Child B – 141 (39%) and in Child C – 122 (34%) patients, respectively. We defined the presence of anemia at Hb value below 130 x 10*9 g/L for men and below 120 x 10*9 g/L for women. Cases were divided by severity into: mild with a value up to 100 x 10*9g/L, moderate with a value between 80-100 x 10*9 g/L, and severe with a value below 80 x 10*9 g/L. Lower reference limit for Er count was 4.4 x 10*12/L for both sexes.

The type of anemia was defined according to MCV (mean corpuscular volume) as: microcytic with a value below 80 fl, normocytic with a value between 80-100 fl and macrocytic with a value above 100 fl. [StatPearls[Internet] https://www.ncbi.nlm.nih.gov/books/NBK545275/.].

Results were analyzed by Crosstabulation and Pearson-Chi Square test to test hypotheses about the distribution of qualitative (categorical) data. ANOVA was used to compare variances between means and standard deviation (SD) of different groups. Kolmogorov-Smirnov test to check the normal distribution of the data and Mann-Whitney test to compare two samples or groups that are not normally distributed were used. The results were processed statistically with IBM SPSS 26 and Exel statistics. A value of $p < 0.05$ was accepted as a level of significance.

RESULTS

Overall, 258 (71%) patients were diagnosed with anemia, regardless of its severity and stage of disease. The incidence in the study population increased significantly with Child-Pough score (Figure 1).

In 160 (62%) of all those with anemia, it was mild. A statistically significant difference was found in the three Child groups according to the occurrence and severity

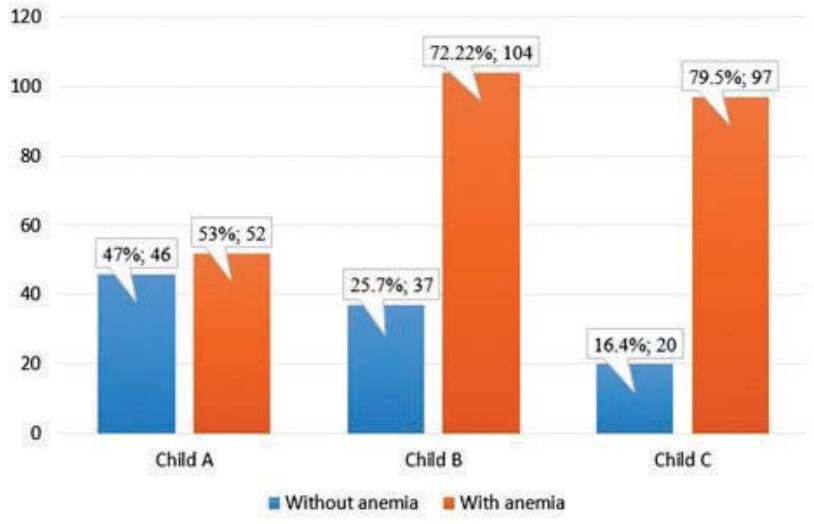

Fig. 1. Distribution of cases with and without anemia according to Child-Pough

of anemia. Cases of mild anemia predominated in all three Child-Pough groups. Those with moderate and severe anemia were mainly associated with Child B and C (F 29.211 df 6 p = .000) (Table 1).

The most common was the normocytic anemia found in 135 (52.3%) cases, followed by macrocytic – 88 (34.1%) cases and the rarest was the microcytic anemia – 35 (13.56%) cases. The normocytic cases were mostly mild, and macrocytic were mainly mild and less often moderate. Cases of microcytic anemia were mostly severe and less often moderate. The obtained results showed a significant difrence between the type of anemia and its severity (F 63.595 df 9 p = .000) (Table 2).

It was found that the incidence of macrocytosis was significantly more common in the alcoholic population. The result shows a statistically significant difference between the two groups (df 3 F 47.129 p = .000) (Figure 2).

Alcoholic etiology was established in 104 out of 116 cases with macrocytosis with or without anemia (89.9%). The result confirms that the presence of macrocytosis is associated with an alcoholic etiology of the disease (F 47.129 df 3 p = .000). Mean value of MCV in the alcoholic group was 97.52 ± 10.62 (95% CI: [96.23-98.80] ± 1.28; ± 1.3%) and in the non-alcoholic group – 88.84 ± 10.34 (95% CI: [86.80-90.87] ± 2.0; ± 2.3%). The result shows a statistically significant difference between the groups (F 48.656 df 1 p = .000). With increasing Child-Pough score, the value of Hb and Er count significantly decreases (df 2 F 15.039 p = .000, respectively df 2 F 34.861 p = .000), and the value of MCV increases (df 2 F 11.232 p = .000). The decreasing value of Hb showed no significant relation with increasing MELD Na (df 32 F 1.025 p = .434). Er count significantly decreased with increasing MELD Na (df 32 F 2.32 p = .000), and MCV value is close to significance (df 32 F 1.459 p = .056) (Table 3).

Table 1. Distribution of cases according to occurrence and severity of anemia and Child-Pough stage

Anemia	Child A N = 98	Child B N = 144	Child C N = 122	Total
No	46 (44.7%)	37 (35.9%)	20 (19.4%)	103
% в Child	46.9%	26.2%	16.4%	28.5%
Mild	37 (23.1%)	64 (40%)	59 (36.9%)	160
% в Child	37.8%	45.4%	48.4%	44.3%
Moderate	12 (18.3%)	24 (36.9%)	24 (44.6%)	65
% в Child	12.2%	17%	23.8%	18%
Severe	3 (9.1%)	16 (48.5%)	14 (42.4%)	33
% в Child	3.1%	11.3%	11.5%	9.1%

Table 2. Distribution of cases according to the type of anemia and its severity

Anemia	Normocytic	Macrocytic	Microcytic	Total
Mild	93 (58.1%)	59 (36.9%)	8 (5%)	160 (62%)
Moderate	28 (43.1%)	24 (36.9%)	13 (20%)	65 (25%)
Severe	14 (42.4%)	5 (15.2%)	14 (42.4%)	33 (13%)
Total	135(52.3%)	88 (34.1%)	35 (13.56%)	N = 258

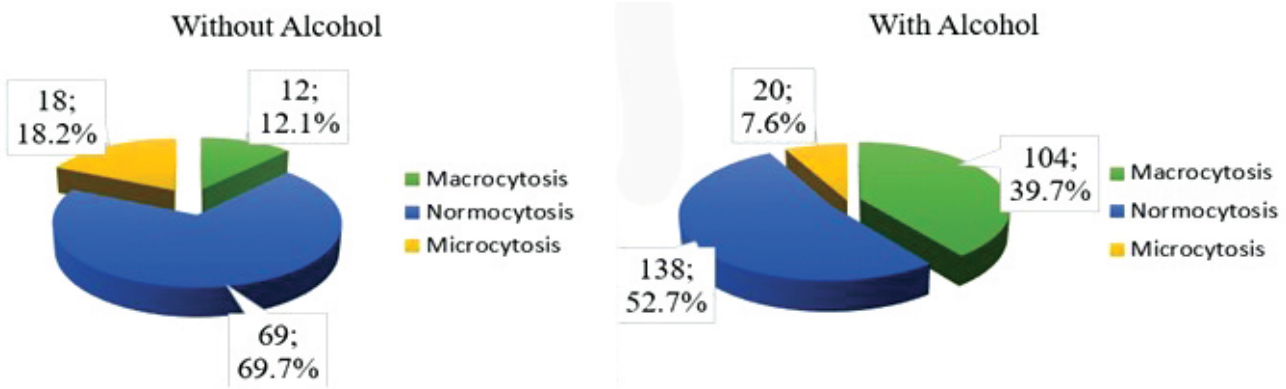

Fig. 2. Relationship between MCV and etiology

Table 3. The values of hematological indicators in the studied groups

Stage	Value	Hb g/L	Er 10*12/L	MCV fl	MELD Na
Child A (N = 98)	Mean ± SD	121.27 ± 21.66	3.96 ± .716	91.77 ± 10.66	9.54 ± 2.75
	Minimal	56	2.1	62	6
	Maximal	164	6.16	114.5	19
	95% CI:	116.98–125.55	3.81–4.10	89.65–93.88	8.99–10.08
		± 4.28 (± 3.5%)	± 0.14 (± 3.6%)	± 2.11 (± 2.3%)	± 0.54 (± 5.7%)
Child B (N = 141)	Mean ± SD	109.90 ± 23.09	3.48 ± .740	94.45 ± 12.02	13.6 ± 4.88
	Minimal	46	1.37	59.5	6
	Maximal	170	5.46	129	30
	95% CI:	106.29–113.67	3.35–3.60	92.48–96.41	12.80–14.39
		± 3.77 (± 3.4%)	± 0.12 (± 3.5%)	± 1.96 (± 2.1%)	± 0.79 (± 5.9%)
Child C (N = 122)	Mean ± SD	105.25 ± 20.72	3.14 ± .702	98.65 ± 9.70	22.3 ± 6.5
	Minimal	51	1.25	68	9
	Maximal	144	5.23	126	40
	95% CI:	101.57–108.92	3.01–3.26	96.92–100.37	21.14–23.45
		± 3.67 (± 3.7%)	± 0.12 (± 4.0%)	± 1.72 (1.7%)	± 1.15 (± 5.2%)

Child-Pough score in cases without anemia was 7.44 ± 2.41 (95% CI:[6.97-7.90] ± 0.46; ± 6.3%), and with anemia was 8.76 ± 2.39 (95% CI: [8.46-9.05] ± 0.29; ± 3.3%) with significant difference between groups (Mann-Whitney: Z-4.799; Asimp. sign. 2-tailed: p = .000) (Figure 3).

MELD Na in cases without anemia was 13.80 ± 6.94 (95% CI: [12.46-15.14] ± 1.34; ± 9.7%), and with anemia was 16.09 ± 7.25 (95% CI: [15.20-16.97] ± 0.88; ± 5.5%) with significant difference between groups (Mann-Whitney: Z-3.097; Asimp. sign. 2-tailed: p = .002) (Figure 3).

DISCUSSION

The most common hematological abnormality in the studied population was the presence of anemia in 258 (71%) of the cases. The results are similar to those of other authors, and the frequency found by them is 81% [8], 70.1% [6], 66% [3], 57.8% [9]. The largest number of identified cases of anemia were mild in 160 (62%) of them, which was also confirmed by other authors, regardless of the different frequency indicated in their results: 41.3% [6], 71.2% [9]. As the Child-Pough stage increased and liver function worsened, the incidence of anemia in the study population increased from 53% in Child A, 72.22% in Child B, to 79.5% in Child C, respectively, and the results obtained were comparable with another study where the same was 57.9%, 80.9% and 87.5%, respectively [10]. The Hb value and number of Er significantly decrease with increasing Child-Pough stage. Moderate and severe anemia was found most frequently in Child B and C cases, which is comparable to findings reported by other authors [6, 3, 10, 11]. A decrease in Hb was associated with

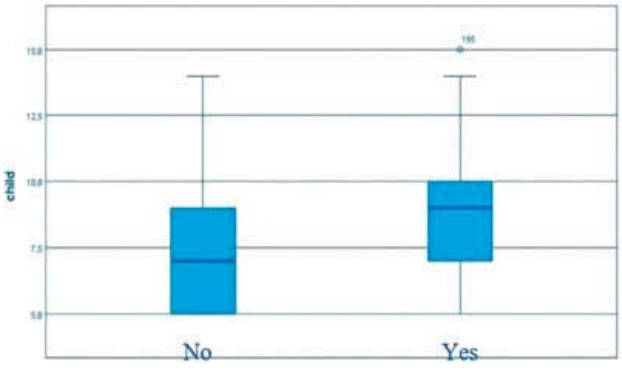

Fig. 3. Child-Pough score in cases without and with anemia

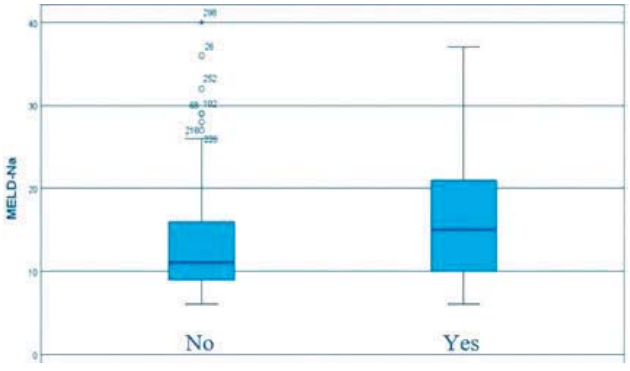

Fig. 4. MELD Na in cases without and with anemia

an increase in MELD Na with no significance. The obtained result differs from other studies that establish an absolute relationship with it [3, 5, 9, 10, 11]. Only the Er count showed absolute significance in the direction of both scores and in previous studies, it was found to correlate better with impaired liver function than the Hb value [12, 13]. A significant difference was found in the MELD Na value in cases with and without anemia. In our study, the value in anemic cases was 16.09 ± 7.25, which differs from other studies that indicate a value above 12 as borderline [3, 9].

Severe anemia was found in 33 (13%) of the studied cases and was mainly associated with Child B and C. Other researchers established a different frequency in their studies: 20.1% [9], 17.3% [14], 7.5% [15].

The reason for the observed differences is most likely related to the number of included cases, the different etiology and stage of presentation, as well as the different definition of severe anemia cases. Normocytic anemia was most common in the study population at 135 (52.3%), followed by macrocytic and microcytic. The obtained result corresponds to the data of other studies, in which normocytic anemia is also the most common in the cirrhotic population at 52% [16], 58.97% [17], 46% [8], 39.4% [18] of the cases studied. Its appearance is associated with the systemic inflammatory response and the release of various proinflammatory cytokines, suppressing bone marrow function [1]. Microcytic anemia was found in 35 (13.56%) cases. The result is consistent with another study:13.3% [14], but significantly different from others with a higher frequency in the cases studied by them: 22.6% [15], 33.3% [16], 40% [8], 43.8% [10]. The most likely reason for the available differences is related to different clinico-epidemiological profiles of the studied patients. On the other hand, in our cases, it is conditionally acceptable that microcytosis is associated with iron deficiency, without considering the other biochemical indicators related to iron metabolism. The main cause of the appearance of microcytic anemia in cirrhosis is acute or chronic bleeding from the GIT, a manifestation of portal hypertension associated with the appearance of iron deficiency. On the other hand, the systemic inflammatory response and impaired regulation of iron metabolism lead to a relative iron deficiency, the result of which is also manifested in normocytic or microcytic anemia [1]. The study found that microcytic anemia could be associated with the presence of esophageal varices [15], in contrast to other researchers who believed that it was mainly observed in the compensated stage [2, 10] and could be a predictor of decompensation [2]. Macrocytic anemia was found in 88 (34.1%) of the people examined. A high incidence of macrocytosis was associated with the leading alcohol etiology in 262 cases, of which 104 (39.7%) had an MCV above 100fl, while in all other etiologies in 99 cases, this was observed only in 12 (12.12%) of them, which was also in compliance with data from other studies [19, 20]. The incidence of macrocytosis among alcohol abusers ranges from 64-84.5% [19], and MCV above 100 fl has been found to be an important predictor of alcohol etiology of chronic liver disease, regardless of the presence of anemia. In our study, 28 (24.14%) patients had macrocytosis with no anemia present.

A significant association was found between the increase in MCV and the Child-Pough score, which is related to the underlying alcohol etiology and severity of liver disease [21, 22, 23]. With MELD Na it is almost significant, unlike other authors who confirm the absolute significance [11, 20].

We found a statistically significant difference in the measured values of MCV for cases with alcoholic and non-alcoholic etiology [22]. The established sensitivity and specificity of MCV for alcohol was 93% and 72% by other authors [23].

The limitations of our research were related to the fact that it was conducted entirely retrospectively, single-center. Even though the number of cases in the study sample was relatively large, it was largely heterogeneous in its structure, posing bias to the results obtained.

CONCLUSION

The presence of anemia is a common hematological manifestation in cases with liver cirrhosis. The high frequency is associated with late diagnosis and a large proportion of decompensated patients at the time of their diagnosis. Cases with mild anemia predominate. The high proportion of macrocytosis in the studied population corresponds to a predominant alcohol etiology. The establishment of this anemic syndrome in patients with risk factors for chronic liver disease requires its inclusion in the differential diagnosis plan.

Conflict of interest statement: *The authors declare no conflicts of interest related to this work.*

Funding: *The authors did not receive any financial support from any organization for this research work.*

Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki.*

REFERENCES

1. Marginean CM, Pirscoveanu D, Popescu M, et al. Diagnostic Approach and Pathophysiological Mechanisms of Anemia in Chronic Liver Disease – An Overview. Gastroenterology Insights. 2023; 14(3):327-341.
2. Paternostro R, Kapzan L, Mandorfer M, et al. Anemia and iron deficiency in compensated and decompensated cirrhosis: Prevalence and impact on clinical outcomes. J Gastroenterol Hepatol. 2020;35(9):1619-1627.
3. Scheiner B, Semmler G, Maurer F, et al. Prevalence of and risk factors for anaemia in patients with advanced chronic liver disease. Liver Int. 2020;40(1):194-204.
4. Bizid S, Yacoub H, Mohamed G, et al. Does Anemia Have a Potential Effect on Type 2 Hepatorenal Syndrome? Can J Gastroenterol Hepatol. 2020; (2):1-5.
5. Pompili E, Baldassarre M, Zaccherini G, et al. Low haemoglobin level predicts early hospital readmission in patients with cirrhosis and acute decompensation. JHEP Rep. 2023 Feb 11;5(5):100698.
6. Ren H, Li H, Deng G, et al. Severe anemia is associated with increased short-term and long-term mortality in patients hospitalized with cirrhosis. Ann Hepatol. 2023 Aug 27;28(6):101147.
7. Macías-Rodríguez RU, Torre A. Diagnostic approach to persistent hepatic encephalopathy. Rev Gastroenterol Mex. 2011 Oct-Dec;76(4):345-52.
8. Rahman MM, Hossain L, Ali H, et al. Abnormal Haematological Indices in Cirrhosis in a Tertiary Care Hospital. Saudi J Med, 2022;7(11): 555-557.
9. Sharma Raj, Sharma Ric, Remya SR.Unveiling the Link: Exploring the Impact of Anaemia on the Severity of Chronic Liver Disease in Patients at A Tertiary Care Hospital National Journal of Medical Research 2023 June 13; (2): 44-49.
10. Rashidi-Alavijeh J, Nuruzade N, Frey A, et al. Implications of anaemia and response to anaemia treatment on outcomes in patients with cirrhosis. JHEP Rep. 2023 Jan 28;5(4):100688.
11. Singh S, Manrai M, V S P, et al. Association of liver cirrhosis severity with anemia: does it matter? Ann Gastroenterol. 2020 May-Jun;33(3):272-276.
12. Xie X, Wang L, Yao M, et al. Correlation between red blood cell count and liver function status. Zhonghua Gan Zang Bing Za Zhi. 2016 Feb;24(2):119-22.
13. Berad A, Chand V. Study to compare hematological parameters in alcoholic and non-alcoholic individuals. Natl J Physiol Pharm Pharmacol 2019;9(12):1176-1179.
14. Joshi D, Akram M, Das K, Kala M. A Cross-Sectional Study of the Haematological Profile of Patients With Chronic Liver Disease (CLD). Cureus. 2023 Jun 5;15(6):e40003.
15. Yan Xu, Wang W, Zhao D. Features of anemia in patients with alcoholic liver cirrhosis. J of Clin Hepatol 2022; (12): 1806-1812.
16. Jain D, Aggarwal HK, Rao A, et al. Hematological spectrum in patients with alcoholic liver cirrhosis: a model of end-stage liver disease score based approach. Int J Adv Med 2016;(3):234-40
17. Lahari J, Usmani MH, Kapur KS, Shukla AK. Clinical and Haematological Abnormalities in Decompensated Chronic Liver Disease Patients. J Assoc Physicians India. 2022 Apr;70(4):11-12.
18. Jose FA, Jayaraj PM, Chethan G. Anemia in chronic liver disease and liver failure in adults – a clinical study. International Journal of Contemporary Medical Research 2020;7(2):B33-B36.
19. Morgan MY, Camilo ME, Luck W, et al. Macrocytosis in alcohol-related liver disease: its value for screening. Clin Lab Haematol. 1981;3(1):35-44.
20. Kaur J, Kaur N, Kaur J, et al. A Study on Haematological Manifestations in Patients with Chronic Liver Disease in a Tertiary Care Hospital of North India. J Evid Based Med Healthc 2021;8(25):2222-2228.
21. Manrai M, Dawra S, Kapoor R, et al. Anemia in cirrhosis: An underestimated entity. World J Clin Cases. 2022 Jan 21;10(3):777-789.
22. Mangal AK, Sharma D, Kumar P, et al. To Study Mean Corpuscular Volume in Alcoholic Liver Disease Patients and to Compare with Child-Pugh Score to Predict the Severity. J Assoc Physicians India. 2023 Jan;71(1):1.
23. Tanriverdđ Ö, Ger E , Uzunoğlu S, et al. Determination of the Role of Mean Corpuscular Volume Level on the Diagnosis of Alcoholic Liver Cirrhosis and Investigation of Its Effect on the Prognosis. Fırat Tıp Dergisi 2008;13(1): 49-52.